

Emerging Topics in Gastroenterology



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KEYWORDS

- Microbiome • Probiotics • Fecal transplant • Cyclic vomiting
- Eosinophilic esophagitis • Microscopic colitis

KEY POINTS

- Genetic variations, diet, stress, and medication use have all been demonstrated to affect the composition of the microbiota in the gastrointestinal tract. Aging may lead to changes in physiology that impact gastrointestinal bacteria, potentially resulting in somatic symptoms related to a disordered microbiome.
- Fecal microbiota transplantation (FMT) has been shown to significantly alter the composition of the recipient's gut microbiome.
- Cyclic Vomiting Syndrome episodes are often triggered by emotional stress or antecedent viral illnesses. CVS is a diagnosis of exclusion, as it lacks any identifying radiological or laboratory abnormalities.
- Eosinophilic esophagitis (EE) is an increasingly-recognized cause of dysphagia and food impaction as well as infant feeding problems.
- Microscopic colitis (MC) is microscopic inflammation of the colonic mucosa that can cause chronic, watery, non-bloody diarrhea, abdominal cramping, and pain. The cause of MC is unclear and it can only be diagnosed through biopsy of the colonic mucosa.

GASTROINTESTINAL MICROBIOME AND PROBIOTICS

Researchers estimate that more than 100 trillion bacteria representing more than 600 different phylotypes can be found within a healthy human gut.¹ Additionally, more than 30 different fungal species may also be found in humans, depending on gender and stage of life.² These bacteria and fungi make up a community of microorganisms that lives in symbiosis with humans, engaging in numerous diverse interactions that influence health. Though the gastrointestinal (GI) microbiome undoubtedly interacts with the human body, there is much that is unknown about the formation, maintenance, and impact that the microbiome has on health and disease.

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New evidence suggests that the microbiome begins forming during the fetal period either through translocation of bacteria from maternal circulation or colonization via bacterial ascension from the vagina.^{3,4} The method of delivery and the first few days of life significantly modify the microbiome composition.⁴ Early diet plays a key role in establishing a colony of good bacteria as human milk oligosaccharides found in breast milk stimulate the growth of key bacteria. Interestingly, randomized trials have demonstrated that the consumption of human milk oligosaccharide analogues, even by adults, can improve the microbiome by stimulating the growth of bifidobacteria.⁵

After establishment, the microbiome continues to evolve in composition and function throughout the first few years of life. During this period, enteric neurons, immunologic factors, and the microbiome itself interact through complex signaling pathways to establish a homeostatic environment in the GI tract.⁶ By age 3 years, the microbiome takes on a composition with characteristics that remain generally consistent through much of adulthood.⁴ However, many events can shift microbiome composition and function in ways that may ultimately affect health. For example, exposure to antibiotics in early childhood may lead to lifelong changes in the composition of the microbiome.^{7,8} Also, as individuals choose a more restricted diet that eliminates specific animal or plant sources of food, the substrates available for bacteria within the GI system can change dramatically. Changing substrates may create new patterns of bacterial growth and changes in the diversity of the microbiome.⁹ Genetic variations, diet, stress, and medication use have all been demonstrated to affect the composition of the microbiota in the GI tract.⁸ Aging may lead to changes in physiology that affect GI bacteria, potentially resulting in somatic symptoms related to a disordered microbiome.^{10,11}

Research is now focusing on the impact that an altered microbiome has on an individual's health and symptomatology. When the composition of the microbiome shifts, individuals may begin to experience specific pathologic symptoms. For example, in patients with irritable bowel syndrome, studies suggest that alterations in bacterial composition are associated with changes in epithelial barrier dysfunction, visceral hypersensitivity, and GI motility.^{12,13}

However, GI symptoms, such as diarrhea, constipation, bloating, and abdominal pain, are no longer thought to be the only manifestations of a disordered microbiome. Dysbiosis, a condition wherein the healthy microbial structure of the GI tract is disturbed, has been postulated to be an inciting event or contributing factor to the development or worsening of metabolic disease, mental health, neurologic disease, and cancer, among other conditions.^{12,14,15} For instance, children who are raised in homes with pets have alterations in their microbiome that may be a link to protection from developing allergic diseases and respiratory virus infections.⁷ Furthermore, studies of individuals with atherosclerosis demonstrate that those with and without disease have significantly different bacterial species that predominate in their GI microbiome.¹⁶ The combination of a specific microbiome composition with a diet that provides a specific digestive substrate may result in the synthesis of trimethylamine-N-oxide, which has been identified as a risk factor for major cardiovascular events.¹⁶ Similarly, in 1 study, the gut microbiome composition was found to be more predictive of type 2 diabetes disease severity than the body mass index.¹⁷ The microbiome is also different in obese and lean individuals.^{18–20} These observations raise interesting questions for future research. Does the composition of the microbiome drive disease or does the disease state alter the milieu of the environment such that the microbiome composition changes? What is the clinical significance of knowing about an alteration? Can diagnostic strategies or treatment options be developed that allow clinicians to partner with the microbiome to improve disease outcomes?

Although metagenomics and emerging techniques targeted at taxonomic identification of gut bacterial composition have significantly increased knowledge of the GI microbiome, little is known about how to apply these observations to the diagnosis and treatment of clinical disease. Many associations are postulated, but few evidence-based recommendations can be made.

Nonetheless, probiotics have gained popularity as a potential source of restoring an ideal GI microbiome to improve symptoms, prevent illness, and treat disease. A meta-analysis of randomized controlled trials demonstrated that probiotic supplementation significantly improved low-density lipoprotein cholesterol levels, which may suggest a route for improving cardiac risk factors beyond current pharmacologic interventions.²¹ Further, modulation of the microbiome through administration of probiotics has been demonstrated to help some individuals improve tolerance of medications such as metformin.²² Several studies have suggested improved behavioral symptoms in children on the autism spectrum after administration of probiotics. The mechanism of action is postulated to be the result of alterations in neurochemical signals from bacteria in the gut that are transmitted through the microbiota-gut-brain axis.²³ Although these results are encouraging, they are very preliminary and are far from ready for widespread clinical implementation.

Probiotics have even been studied as a potential source of performance enhancement for athletes. Using mouse models, researchers have shown that the physical and emotional stress that occurs during exercise may alter the microbiome. This can result in a change of the neurotransmitters released by the gut that travel via enteric neurons to the brain. The changes in serotonin, dopamine, and other neurochemicals may lead to fatigue and mood disturbance, and manifest as underperformance. The question remains, however, if probiotic supplementation can positively affect the gut microbiome and result in the ideal neurotransmitter signals to optimize performance during training or competition.²⁴

Although probiotics have been touted to improve the immune system, help prevent bowel disease, treat conditions ranging from lactose intolerance to hypertension, and even alleviate postmenopausal symptoms, much of the evidence of effectiveness is anecdotal.²⁵ Published clinical trials have been limited and show mixed results. For example, the use of probiotics to treat chronic GI diseases such as irritable bowel syndrome seems to make pathophysiologic sense, yet data are mixed when implemented clinically.^{12,26} Similarly, a review of 2900 subjects in 30 trials demonstrated that probiotics significantly reduced nosocomial infections, including ventilator-associated pneumonia in critically ill subjects. However, no reduction was noted in mortality or length of stay, making clinical application of these findings difficult.²⁷

Moreover, as a supplement, probiotics lack standard formulations and dosages, which further impairs clinical use even when research has demonstrated effectiveness. For example, probiotics have been shown to be effective for the prevention and treatment of antibiotic-associated diarrhea, yet the lack of standardization of supplements makes clinical implementation of this knowledge difficult.²⁸ Research suggests that a diverse diet, rich in fiber, provides an optimized environment to stimulate growth and activity of the ideal microbiome. This may be as effective as supplementation with probiotics, which may or may not contain the ideal bacteria needed by a given individual.^{8,10}

FECAL MICROBIOTA TRANSPLANTATION

Collectively, these organisms that make up the gut microbiome have more than 100 times more genes than their human host. Emerging research suggests these microorganisms and their collective genome may play an important role in metabolic health

and disease.²⁹ The gut microbiome can be altered in multiple ways. In addition to the ingestion of probiotics and prebiotics, the transplantation of fecal matter can also alter the gut microbiome. Attempts to change an individual's gut microbiome go back as far as the fourth century when the first fecal transplant was recorded for the treatment of severe diarrhea.²⁹

Fecal microbiota transplantation (FMT) has been shown to significantly alter the composition of the recipient's gut microbiome. Randomized controlled trials have demonstrated the success of FMT in the treatment of recurrent or refractory *Clostridium difficile* infection, which is the only application of FMT approved by the US Food and Drug Administration (FDA).^{29–31} Research continues into the best delivery method for FMT in the treatment of *C difficile* infections, as well as the use of FMT in several other conditions, including vancomycin-resistant *Enterococcus* (VRE) infection and the treatment of obesity and metabolic syndrome.^{29–33}

FMT in *C difficile* infection has been highly effective (83%–100%) and rarely associated with major adverse events.³¹ However, its use is limited by practical barriers and stigma. Currently, donor stool is collected, processed, and suspended in sterile saline.³⁰ It is then delivered via nasogastric tube, upper endoscopy, or in a retrograde fashion via colonoscopy, all with similar success rates.³¹ These methods all expose patients to risk, as well as discomfort. Delivery of FMT using oral capsules of frozen fecal material is being investigated at Massachusetts General Hospital.³⁰ Subjects are given 15 capsules on 2 consecutive days (30 capsules total). To date, 202 subjects have been treated and 180 have had documented follow-up. *C difficile* infections resolved in 82% of subjects after a single treatment and 91% with 2 treatments. These rates are in line with endoscopic and colonoscopic administration of FMT. Though promising, more study is needed to document long-term safety.

FMT is also being studied for VRE, as well as obesity and metabolic syndrome. Data are still primarily from animal studies. Studies of FMT in VRE-colonized mice have shown some promise, but case studies in human subjects have not been as successful.^{32,33} Studies conducted in rodents have suggested that FMT has the ability to alter the metabolic phenotype of the recipient.²⁹ Mice receiving an FMT from an obese rat demonstrated increased adiposity compared with those receiving it from a lean rat. One published study examined the efficacy of FMT in metabolic syndrome in humans.²⁹ The study involved 18 subjects and, although there was no significant body mass index difference between groups at 6 weeks, there was a statistically significant increase in insulin sensitivity. [Clinicaltrials.gov](https://www.clinicaltrials.gov) lists several other ongoing trials involving FMT. Studies in the United States, Italy, China, and Canada are examining the effect of FMT on body weight reduction, glucose homeostasis, type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease.

Important research questions about FMT exist. Who is the ideal donor, who is the ideal recipient, how long do gut microbiome alterations persist, and does FMT have applications beyond treatment of GI infections? These questions and more are subject to hypothesis generation and continuing research.

CYCLIC VOMITING SYNDROME

Cyclic vomiting syndrome (CVS), first described in 1882, is a poorly understood functional GI disorder characterized by recurrent bouts of nausea and severe vomiting, with a return to baseline health between episodes. It was long thought to occur primarily in children but is now known to occur in adults as well. The median age of onset is between 4 and 7 years, and the incidence is estimated to be 3.2 per 100,000 children per year.³⁴

The underlying causes of CVS are unknown but believed to be similar to other triggered, episodic disorders such as migraine, epilepsy, and panic disorders.³⁵ Some cases are believed to be related to mitochondrial dysfunction and many investigators believe CVS is a form of abdominal migraine because cases are frequently associated with migraine headaches.³⁴ Approximately 30% of children with CVS will continue to experience episodes into adulthood.³⁴ Children with CVS will typically have 8 to 12 attacks per year characterized by severe vomiting, often with at least 4 episodes per hour.³⁴ An attack will usually last 20 to 48 hours in children, longer in adults. Vomiting often begins in the early morning hours and more than 70% of episodes are associated with abdominal pain. Episodes are often triggered by emotional stress or antecedent viral illnesses. CVS is a diagnosis of exclusion because it lacks any identifying radiological or laboratory abnormalities.

Treatment of CVS consists of 2 parts: aborting acute attacks and prophylaxis of future attacks. Acute treatment is aimed at controlling nausea and vomiting, and addressing fluid status and electrolyte imbalances. In many ways, acute treatment is similar to that for acute migraine. Patients should lie down in a quiet, dark room. 5-Hydroxytryptamine type 3 (5-HT₃) receptor antagonists such as ondansetron are the mainstay of treatment of nausea and vomiting.³⁴ Triptans can also be tried, especially in attacks associated with migraine headaches. Isotonic saline boluses are used to restore hydration, followed by dextrose-containing solution until the patient can tolerate oral intake. Patients rarely require hospitalization unless they have lost greater than 5% fluid volume, have been anuric for 12 hours or more, have severe metabolic or electrolyte disturbances, or are unable to control emesis.³⁴ Amitriptyline and beta-blockers have been the mainstays of prophylactic treatment, though recent studies have shown promising, and improved, results with topiramate.^{34,36} Psychological factors also play a role in CVS, both as a trigger and as a cause of worsened disability from the disorder.³⁷ Therefore, a biopsychosocial approach that also uses psychotherapy can be useful in CVS.

There is a high incidence of clinical anxiety in children with CVS. Children with diagnosed or suspected CVS should be screened for anxiety and, if present, treated appropriately.³⁸ Treatment of coexisting anxiety can help improve the child's coping ability, if not the disorder itself. In adults, an increasingly identified cause of CVS is overuse of cannabis.³⁴ Low dose use of cannabis can have antiemetic effects, but chronic, frequent use can have the opposite effect. Cannabinoid hyperemesis syndrome is characterized by cyclic and recurrent vomiting, abdominal pain, and the unusual feature of taking frequent, hot showers that seem to ameliorate symptoms. Cessation of cannabis use usually aborts the attack.

EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis, once considered to be a rare condition, is increasingly diagnosed.³⁹ It is unclear if eosinophilic esophagitis is increasing in prevalence or if it was previously under-recognized. The diagnosis is made by observing 15 eosinophils per high-power field on a biopsy specimen of the esophagus. The male to female ratio is 3:1 and it is most common in white men.⁴⁰

Eosinophilic esophagitis can be asymptomatic; it can also cause dysphagia and food impaction. It is reported that up to 54% of patients undergoing endoscopy for a history of food impaction in the esophagus are discovered to have eosinophilic esophagitis.⁴¹ In the absence of a clear reason for dysphagia or esophageal food impaction, a biopsy of the esophagus should be strongly considered to aid in making a diagnosis.

The cause of eosinophilic esophagitis is thought to be immune-mediated and the antigens responsible for the immune response seem to be food-based. There are several interesting theories on why eosinophilic esophagitis seems to be increasing in prevalence. Many of these theories revolve around the hygiene hypothesis. The hygiene hypothesis postulates that a lack of early childhood exposure to various microorganisms and allergens suppress the natural development of the immune system. Lack of exposure to these agents may lead to defects in immune tolerance. Antibiotic exposure during infancy, food allergy, and a lack of breastfeeding are associated with eosinophilic esophagitis.⁴² There may be a positive family history of eosinophilic esophagitis or a family history of atopic disorders such as asthma, eczema, or anaphylaxis.⁴³

On visual inspection of the esophageal mucosa of patients with eosinophilic esophagitis, the mucosa may demonstrate small white specks that represent eosinophilic exudates. There may also be evidence of strictures, linear furrows in the mucosa, and mucosal edema.⁴³ When the endoscopist performs a mucosal biopsy, she or he may notice some resistance when taking the biopsy specimen; this has come to be known as the tug sign.⁴⁴ Linear tears in the esophagus may occur with minimal trauma during passage of the endoscope. A barium swallow complements the evaluation of eosinophilic esophagitis because some strictures in this condition may be lengthy and tapered and, therefore, may not be evident on direct observation with the endoscope.⁴³

The most effective treatment of eosinophilic esophagitis is an elemental diet consisting of amino acids and the elimination of food antigens.^{45,46} This dietary regimen almost completely eliminates the symptoms of eosinophilic esophagitis and histologic abnormalities. Unfortunately, many patients cannot abide by a strict elemental diet. Using skin-prick allergy testing, patch testing, and serum IgE testing to identify specific allergens and guide the focused elimination of foods has had disappointing results.⁴⁵ Another option is to empirically avoid the 6 most common allergenic foods: wheat, milk, soy, nuts, eggs, and seafood, the so-called 6-food elimination diet.^{43,46} In general, acid suppression with proton pump inhibitors and histamine blockers does not help, though they are frequently prescribed.⁴³ Though not approved by the FDA, a fluticasone metered-dose inhaler and a viscous preparation of liquid budesonide have been tried in some research studies with some evidence of symptom and histologic improvement.^{40,43,45,46} Esophageal dilation may be required in some patients with luminal narrowing due to eosinophilic esophagitis.^{43,45,46} Antireflux surgical procedures have not been shown to help.⁴³

Current evidence does not indicate that eosinophilic esophagitis is a premalignant syndrome and it does not seem to shorten lifespan. However, it does seem to be a chronic disease and complications such as esophageal strictures may develop.⁴³

Eosinophilic esophagitis can also cause infant feeding problems. Symptoms include a wide variety of nonspecific feeding problems, such as vomiting and failure to thrive, in infants. Children may suffer from nausea, vomiting, and abdominal pain. Teenagers and young adults can suffer nausea, vomiting, and abdominal pain, as well as food impaction, dysphagia, and reflux symptoms.⁴⁷ It has been proposed that children, adolescents, and young adults with eosinophilic esophagitis learn to compensate for their symptoms by eating slowly, chewing carefully, cutting food into small pieces, and drinking lots of fluids when they eat to lubricate and dilute foods. They may avoid some foods, such as meat and bread, and may avoid eating in public or taking pills. It is postulated that some patients have years and years of silent or subclinical disease by almost unconsciously controlling their symptoms with these techniques.⁴³

MICROSCOPIC COLITIS

As the name implies, microscopic colitis is inflammation of the colon that is only apparent on histologic evaluation of tissue.^{48,49} Symptoms most commonly associated with microscopic colitis are chronic, watery, nonbloody diarrhea and abdominal cramping and pain. Patients may have 5 to 10 watery stools per day. Symptoms can last for days to months or years, or can be intermittent. Bloating, nausea, and rectal urgency may also be present. Rarely, fecal incontinence and weight loss may occur.⁴⁹

A relationship between microscopic colitis and irritable bowel syndrome has been postulated. The relationship of microscopic colitis to inflammatory bowel disease is unclear. There are 2 subtypes of microscopic colitis. The first subtype, lymphocytic colitis, demonstrates an increase in lymphocytes in the mucosa, but the mucosal lining is of normal thickness. In the second subtype, collagenous colitis, lymphocytic infiltration is accompanied by collagen deposition in the mucosa and the mucosal lining may be thicker than usual. Whether these 2 subtypes are distinct entities or phases of the same condition is unclear. An individual may have findings of lymphocytic colitis and collagenous colitis in different parts of the colon.^{48,49}

There are no blood tests, stool tests, imaging studies, or pathognomonic physical examination findings diagnostic of microscopic colitis. It can only be diagnosed with a biopsy of the colonic mucosa. A variety of laboratory tests, including sedimentation rate, peripheral blood eosinophil count, and serum complement levels, may be abnormal in a particular patient, but there are no definitive diagnostic markers.⁴⁸ An increased number of leukocytes may be identified in stool specimens. A few patients may have edema and mucosal erythema or paleness on visual inspection.⁵⁰

The cause of microscopic colitis is unknown. It may be the result of an autoimmune reaction or an abnormal immune response to bacteria, medication, toxins, or noxious agents such as bile acid. The role of genetics is unclear.⁴⁸ A leading theory is that microscopic colitis develops after a bout of bacterial or viral gastroenteritis.⁴⁸ Autoimmune disorders associated with microscopic colitis include diabetes mellitus, celiac disease, thyroid disease, and rheumatoid arthritis.^{48,49} The ingestion of many commonly used medications, such as nonsteroidal anti-inflammatory agents, proton pump inhibitors, histamine (H)-2 blockers, statins, and selective serotonin reuptake inhibitors, have been associated with microscopic colitis, but the causal link is unproven.^{49,51} Risk factors for the development of microscopic colitis are age older than 50 years, female gender, underlying autoimmune disease, cigarette smoking, and use of medications associated with the disease. Children are rarely affected.^{51,52}

Treatment includes discontinuation of tobacco smoking and, if possible, medications that might be related. Avoidance of symptom-inducing foods and beverages and use of symptom control medications, such as anti-diarrheal agents, may be used. Control of any underlying autoimmune disorders may be helpful. In some patients, cholestyramine resin can be helpful.^{53–55} Budesonide rapidly induces symptom improvement but the relapse rate after discontinuation is high.^{49,55,56} Evidence that the use of immune system modulators, anti-tumor necrosis factor (TNF) therapies, or biological agents is lacking and use of these agents should be driven by clinical judgment and balanced against the potential for treatment complications.⁵⁵ It does not seem that microscopic colitis increases the risk of colon cancer.⁵¹

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